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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,788	07/03/2003	George B. McDonald	8105-009-US-CON	6992

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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
05/18/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,788	MCDONALD, GEORGE B.	
	Examiner	Art Unit	
	ERIC S. OLSON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted February 17, 2009 wherein the rejections of record in the previous office action are traversed. This application is a continuation of US application 09/753814, now abandoned, filed January 3, 2001, which claims benefit of provisional application 60/233194, filed September 15, 2000.

Claims 1-16 are pending in this application.

Claims 1-16 as amended are examined on the merits herein.

The following rejections of record in the previous office action are maintained:

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10 and 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDonald et al. (Reference of record in previous office action) in view of Bertz et al. (Reference of record in previous office action)

McDonald et al. teaches that oral administration of the particular topically active corticosteroid, beclomethasone dipropionate (BDP), **alone** in the form of a capsule or **in combination with prednisone** (in the language of instant claim 16) is useful in a method of treating graft-versus-host disease in a human following organ allograft

transplantation or stem cell transplantation for 30 days (see abstract and page 28, 1st paragraph, right column). McDonald et al. also teaches that the subject has damaged tissue in the intestinal mucosa and liver, in the language of claims 3, 4, and 6 (p. 32, table 4). McDonald et al. al. also teaches the effective amount of beclomethasone dipropionate to be administered as 8 mg per day (p. 29, left column, under the heading *Formulation of BDP and Placebo Capsules*), within the range of 4-12 mg/day set by the instant claim 2. McDonald et. al. also discloses that the capsules administered were either uncoated (to dissolve in the stomach) or enteric-coated (to dissolve in the intestine) in the language of instant claim 10(p. 29, left column, under the heading *Formulation of BDP and Placebo Capsules*). McDonald discloses that the treatment was well-tolerated, and that typical side effects of corticosteroids, such as microbial infections, hypercortisolism, and adrenal insufficiency, were not observed during the treatment. (p. 32, left column, first paragraph, under the heading, "Toxicity from Treatment," and p. 33, left column, last paragraph – right column, first paragraph) McDonald et. al. also reveal the aim for the study therein to compare the effectiveness of oral BDP to that of placebo capsules in the claimed method herein, and also to examine the frequency of infection in patients treated with beclomethasone dipropionate. See abstract and the entire article, especially p. 29, left column, first paragraph and right column, 3rd paragraph. McDonald et al. does not expressly disclose the long-term therapy (i.e., 29-56 days) in the claimed method, or therapy wherein administration of the topically active corticosteroid commences at least 29 days post-transplantation.

Bertz et al. discloses a method of treating graft-versus-host disease by administering oral budesonide as a topically active corticosteroid. (p. 1186, left column, second paragraph - right column, third paragraph) At enrollment, patients had a mean time of 30 days since transplantation, with actual times ranging between 10 and 310 days. (p. 1186, left column table 1) The duration of the therapy was between 6-70 days, varying from patient to patient, with no side effects observed in any patient. (p. 1187, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to orally administer BDP alone or with prednisone over the long term (i.e. 29-56 days) starting at least 29 days post-transplantation. One having ordinary skill in the art at the time of the invention would have been motivated to orally administer BDP alone or with prednisone in the long term (i.e. 29-56 days) since the administration of BDP alone or with prednisone for 30 days or les is known according to the prior art, and a subject may not have fully recovered from their condition after 30 days, and further because Bertz et al. discloses that budesonide, which is a similar topically active corticosteroid, can also be administered for the treatment of graft-versus-host disease. Thus, one of ordinary skill in the art would reasonably extend the therapy to the longer period from 30 days or less to 56 days if such treatment is still required after 30 days from the beginning of treatment. One of ordinary skill in the art would reasonably have expected success in administering the therapy for more than 30 days because McDonald discloses that no side effects were noticed in patients administered beclomethasone dipropionate, and furthermore because Bertz et al.

discloses that patients maintained on a similar topically active corticosteroid, budesonide, showed no side effects when maintained on the drug for up to 70 days. In view of these disclosures, one of ordinary skill in the art would have determined that beclomethasone dipropionate could reasonably be administered for a duration of over 30 days due to the observed lack of side effects for topically active corticosteroids. Moreover, determination of the time period of administration is considered well within the skill of the artisan, involving merely routine skill in the art.

Furthermore, it would have been obvious to begin the therapy at least 29 days post-transplantation (for example in patients who are discontinuing prednisone therapy) because many of the patients studied by Bertz et al. are begun on topically active corticosteroid therapy at more than 29 days, in some cases as long as 310 days after transplantation. One of ordinary skill in the art would reasonably have interpreted these results to indicate that patients 29 or more days post-transplantation can be started on topically active corticosteroid therapy with a reasonably expectation of success.

Thus the invention as a whole is *prima facie* obvious over the prior art.

Response to Argument: Applicant's arguments and amendment submitted February 17, 2009 as applied to the above rejection have been fully considered and not been found persuasive to remove the above rejection for reasons of record in the previous office action and additionally as discussed below.

Applicant makes two arguments with respect to the above ground of rejection, firstly that according to the declaration of McDonald submitted March 23, 2007, one of ordinary skill in the art would have considered extending treatment beyond 29 days to

be too risky to contemplate, and secondly that the corticosteroid used by Bertz et al. is completely different from beclomethasone and therefore is non-analogous and cannot be combined with the results disclosed by McDonald et al.

With regard to the first argument, mere conclusory statements made by an interested party (namely the inventor of the instant application) are not dispositive of the issue of obviousness or the state of the art. Whether or not it is true that at the time of the invention those of ordinary skill in the art saw administration of corticosteroids beyond 29 days as being excessively risky, the disclosure of the McDonald et al. reference would be seen as challenging that conclusion and providing a motivation for longer-term administration. According to the declaration, the reason that one of ordinary skill in the art would not have continued administration beyond 29 days is because of the intolerable side effects of long-term systemic corticosteroid administration, for example immunosuppression, diabetes, hypertension, bone loss, muscle weakness, Cushingoid appearance, neuropsychiatric disturbance, and suppression of the hypothalamic-pituitary axis. None of these side effects were observed by McDonald et al. Instead, the topically active corticosteroid therapy disclosed in this reference was well tolerated with no side effects. One of ordinary skill in the art would, upon reading the disclosure of McDonald et al., consider the therapy disclosed by McDonald et al., using a topically active corticosteroid, to overcome the limitations of the prior art as to side effects and to therefore be suitable for long term administration.

With regard to the second argument, McDonald et al. and Bertz et al. both identify their compounds as topically active corticosteroids. Thus one of ordinary skill in the art would have seen them as being analogous, especially since the desirable properties of oral BDP disclosed by McDonald (improved tolerability and absence of side effects) are disclosed as being due to the fact that it is a topically active corticosteroid. Rather than being a "completely different drug" as alleged by Applicant, budesonide would be considered by one of ordinary skill in the art to be a similar and analogous drug by virtue of its being a topically active corticosteroid, and one of ordinary skill in the art would expect it to behave similarly to BDP, with results disclosed for budesonide being applicable to the use of BDP as well.

For these reasons the rejection is deemed proper and made **FINAL**.

Claims 1-10 and 12-16 are rejected under 35 USC 103(a) as being unpatentable over Baehr et. al. (Reference of record in previous office action) in view of Bertz et al. (Reference of record in previous action)

Baehr et. al. teaches that oral administration of the particular topically active corticosteroid, beclomethasone dipropionate, alone in the form of a capsule for 28 days, is a useful method of treating graft-versus-host disease in a human following organ allograft transplantation of human leukocyte antigen mismatched marrow. (p. 1233, right column, under the heading, *clinical efficacy*) Patients entered the study at a mean period of 58 days post-transplantation. (p. 1233, left column, last paragraph) Baehr et. al. also teaches that, in subjects already taking prednisone, "The prednisone dose at

study entry was maintained throughout the study whenever medically possible," (p. 1232. left column, 3rd paragraph) meaning that BDP was administered in conjunction with another prophylactic agent as taught by instant claim 16. Baehr et. al. also teach the use of BDP in subjects who have tissue damage of the intestinal mucosa and liver. Baehr et. al. also teaches the effective amount of beclomethasone dipropionate to be 8 capsules of 1 mg each per day, for a total dose of 8 mg per day, in accordance with instant claim 2. (p. 1232, under the heading, *formulation and dosing of beclomethasone dipropionate*) Although adrenal axis function was reduced in patents receiving BDP, no clinical side effects were observed. (p. 1234, right column, p. 1236, right column, second paragraph) Baehr et. al. also suggest that the purpose of the study is to evaluate whether the oral BDP is a safe effective treatment for the instant disease. See the abstract of Baehr et. al. Baehr et. al. does not explicitly disclose the long-term therapy (i.e. 29-56 days) of the claimed invention.

Bertz et al. discloses a method of treating graft-versus-host disease by administering oral budesonide as a topically active corticosteroid. (p. 1186, left column, second paragraph - right column, third paragraph) At enrollment, patients had a mean time of 30 days since transplantation, with actual times ranging between 10 and 310 days. (p. 1186, left column table 1) The duration of the therapy was between 6-70 days, varying from patient to patient, with no side effects observed in any patient. (p. 1187, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to orally administer BDP alone or with prednisone over the long term (i.e. 29-56 days), beginning at least 29 days after transplantation.

One having ordinary skill in the art at the time of the invention would have been motivated to orally administer BDP alone or with prednisone in the long term (i.e. 29-56 days) since the administration of BDP alone or with prednisone for 30 days or les is known according to the prior art, and a subject may not have fully recovered from their condition after 30 days, and further because Bertz et al. discloses that budesonide, which is another topically active corticosteroid having similar biological effects, can also be administered for the treatment of graft-versus-host disease. Thus, one of ordinary skill in the art would reasonably extend the therapy to the longer period from 30 days or less to 56 days if such treatment is still required after 30 days from the beginning of treatment. Furthermore because Bertz et al. discloses that patients maintained on a similar topically active corticosteroid, budesonide, showed no side effects when maintained on the drug for up to 70 days. In view of these disclosures, one of ordinary skill in the art would have determined that beclomethasone dipropionate or budesonide could reasonably be administered for a duration of over 30 days due to the observed lack of side effects for topically active corticosteroids. Moreover, determination of the time period of administration is considered well within the skill of the artisan, involving merely routine skill in the art.

Thus the invention as a whole is *prima facie* obvious over the prior art.

Response to Argument: Applicant's arguments and amendment submitted February 17, 2009 as applied to the above rejection have been fully considered and not been found persuasive to remove the above rejection.

Applicant's arguments are the same as those made with respect to the rejection over McDonald et al. in view of Bertz et al. above and are not found to be persuasive for the same reasons. Therefore the rejection is deemed proper and made **FINAL**.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over McDonald et. al. (References of record in previous office action) or alternately Baehr et. al. (References of record in previous office action), in view of Bertz et al. (Reference included with PTO-892) in view of, alternately, US patents Lundquist, Brancq et. al., or Benita et. al. (US patents 5843465, 5958431, and 6007826, References of record in previous office action).

The disclosures of McDonald et. al. and Baehr et. al. in view of Bertz et al. is discussed above. The above references do not disclose a method in which the active agent is administered as a pharmaceutical emulsion.

Lundquist, Brancq et. al., and Benita et. al. all disclose pharmaceutical emulsions, and methods for preparing the same from hydrophobic pharmaceutical compounds. (see, for example, claim 1 of Lundquist, claim 1 of Brancq et. al., or claim 1 of Benita et. al.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to orally administer BDP alone or with prednisone as an emulsion, in the manner of claim 11, as disclosed by the aforementioned US patents.

One having ordinary skill in the art at the time of the invention would have been motivated to administer the compound as an emulsion to increase solubility and bioavailability. One of ordinary skill in the art would have reasonably expected success because determination of the optimal dosage formulation is considered well within the skill of the artisan, involving merely routine skill in the art.

Thus the invention as a whole is *prima facie* obvious over the prior art.

Response to Argument: Applicant's arguments and amendment submitted February 17, 2009 as applied to the above rejection have been fully considered and not been found persuasive to remove the above rejection.

Applicant's arguments are the same as those made with respect to the rejection over McDonald et al. in view of Bertz et al. above and are not found to be persuasive for the same reasons. Therefore the rejection is deemed proper and made **FINAL**.

Conclusion

No claims are allowed in this application. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/

Examiner, Art Unit 1623

5/13/2009

/Shaojia Anna Jiang/

Supervisory Patent Examiner, Art Unit 1623